Amendments to the Specification

Please replace the original specification with the substitute specification attached hereto. Per 37 C.F.R. § 1.125, a marked version, showing all changes relative to the prior version, is attached here, beginning on the next page. Amendments have been made on Page 6, line 4; Page 8, line 11; Page 11, line 2; Page 15, Table 1, Compound No. 159; and Page 18, line 8 (**all page references refer to page and line numbers in this preliminary amendment**). A clean version, showing no markings, is attached at the end of this amendment. No new matter is added through any of the amendments.

USES OF MELANOCORTIN-4 RECEPTOR (MC4R) AGONIST PEPTIDES ADMINISTERED BY CONTINUOUS INFUSION

The melanocortin-4 receptor (MC4R) is a G-protein coupled receptor (GPCR). MC4R mediates a signal that it receives from the endogenous melanocortin stimulating hormones (MSH) and the agouti related protein peptide (AGRP) in the hypothalamus. The former peptides are processed from a proopiomelanocortin (POMC) precursor protein produced by the neurons in the arcuate nucleus of the hypothalamus. Those peptides are competitive full agonists for the MC4 receptor. Conversely, AGRP is reported to be either a competitive antagonist or an inverse agonist at the same receptor. This endogenous messenger is also produced and released by neurons in the hypothalamus but distinct from those synthesizing POMC. Together, the melanocortin system is part of the neuronal hypothalamic network regulating energy balance.

It has been proposed that during physiological states characterized by a negative energy balance, AGRP signaling is enhanced and POMC signaling is reduced. Further, those responses are thought to participate in correcting the negative energy balance. Specifically, AGRP signaling would dominate over MSH signaling, resulting in enhanced appetite and decreased energy expenditure via decreased activity of the sympathetic nervous system.

Etiology and pathophysiology of obesity remains a subject of intense study. There are rare examples of obese individuals and obese rodents with mutations of MC4R or POMC genes. Over-expression of an AGRP transgene will also present an obese mouse. There are no examples of over-expression of POMC producing a lean phenotype. This raises the possibility that MC4R may be desensitized during continuous exposure to its agonists. Indeed, there are many examples of GPCRs that are down regulated by chronic exposure to their agonists.

Daily peripheral administration of the MSH agonist melanotan II (MT-II) for at least one week decreases weight gain in rodents, indicating that a peripheral injection of the peptide will trigger the MC4 receptor in the hypothalamus and that a lean phenotype can be realized. Further, such studies suggest no desensitization after intermittent administration. Because those peptides have a short half-life and were only administered

intermittently, it follows that the receptor was also only infrequently occupied and that may have prevented any down regulation or desensitization.

A need exists to find an agonist capable of triggering the MC4 receptor, capable of being administered such that the receptor remains occupied, but without down regulation or desensitization of the receptor. Meeting this need will provide a means to induce weight loss and overcome obesity, a disease that has major debilitating effects on the body.

The present invention provides a method of inducing weight loss in a patient, comprising continuous infusion of an effective amount of an MC4R agonist peptide into the patient. Additionally, the present invention provides a method of treating obesity in a patient, comprising continuous infusion of an effective amount of an MC4R agonist peptide into the patient. Furthermore, the present invention provides the use of an MC4R agonist peptide for the manufacture of a medicament for the treatment of obesity, wherein the medicament is administered by continuous infusion.

The instant invention demonstrates that when the same mass of an MC4R agonist peptide is delivered to patients using two different methods: (1) a single daily bolus subcutaneous administration, or (2) by continuous subcutaneous infusion, the peptide is much more effective when administered continuously than intermittently. Those data suggest that the MC4 receptor can be continuously occupied with an agonist without down regulation or desensitization.

Moreover, a low rate of infusion, for example approximately 2 μg/hr of Ac-D-Arg-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-NH_2 infused into the subcutaneous environment, is sufficient to overcome metabolism and dilution of the peptides to successfully bind the hypothalamic receptor in quantities that would overcome competition by AGRP.

Furthermore, delivery of the peptide via continuous infusion allows the MC4 receptor to remain continuously occupied. Importantly, this overcomes problems associated with bolus injections. For instance, due to short half-life of the MC4R agonist peptide, shortly after a bolus injection is made, the peptide degrades, leaving the receptor open for antagonists or inverse agonists to occupy. Occupation by an antagonist or inverse agonist may not induce weight loss; conversely, it may induce

weight gain. Yet, with continuous infusion of the MC4R agonist peptide, the receptor remains occupied with the agonist. Additionally, potential side effects caused by bolus injections, such as penile erection, may be avoided.

For the purposes of the present invention, as disclosed and claimed herein, the following terms are as defined below.

"Continuous infusion" of an MC4R agonist peptide refers to controlled parenteral delivery of the peptide to a patient for an extended period of time. Administration of the peptide may be accomplished by, but is not limited to, delivery via pump, depot, suppository, pessary, transdermal patch or other topical administration (such as buccal, sublingual, spray, ointment, creme, or gel) using, for example, subcutaneous, intramuscular, intraperitoneal, intravenous, intracerebral, or intraarterial administration.

A pump delivering the MC4R agonist peptide into the body may be implanted in the patient's body. Alternatively, the patient may wear a pump externally, being attached to the patient's body via catheter, needle, or some other connective means. Any pump that is suitable for the delivery of pharmaceuticals to a patient may be used. Examples include pumps such as those disclosed in US Pat. No. 6,659,982.

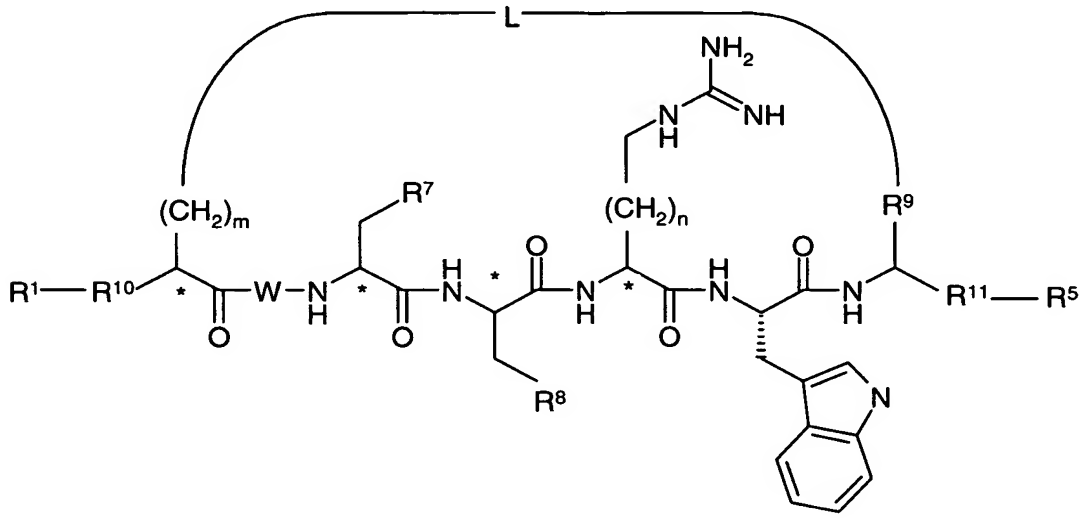
A depot is a biocompatible polymer system containing the MC4R agonist peptide and delivering the peptide over time. Examples include microspheres, microcapsules, nanoparticles, liposomes, a hydrogel, or other polymeric implants. Preferred periods for delivery of agonist by depot include one week, two weeks, and one month periods. If needed, another depot will be delivered to the patient for continued delivery of peptide.

Engineering the MC4R agonist peptide to have a prolonged half-life will also result in continuous delivery of the MC4 receptor agonist to the receptor. Such modifications include conjugations with larger proteins such as albumin, antibody and antigen or chemical modifications that may increase half-life by linking fatty acids, polyethylene glycol (PEG) polymers, and other agents.

An "MC4R agonist peptide" utilized in the instant invention includes any agonist peptide which has affinity for the MC4 receptor. Examples include, but are not limited to, MC4R agonists disclosed in the following art: US Pat. No. 5,674,839; WO 01/52880; WO 03/006604; WO 00/36136; WO 01/00224; WO 01/13112; WO 00/58361; US Pat. No. 6,613,874; WO 02/26774; WO 99/54358; WO 01/74844; WO 02/18437;

WO 98/27113; WO 01/05401; US Pat. No. 5,731,408; and WO 01/85930, which are herein incorporated by reference.

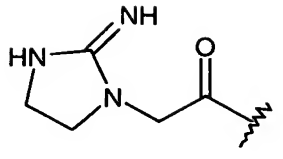
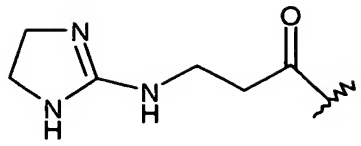
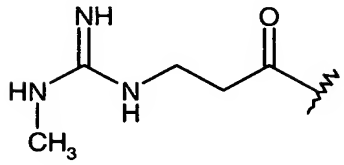
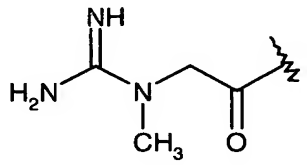
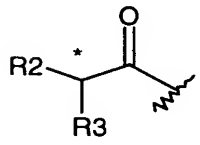
In another embodiment, the MC4R agonist peptide for use in the present invention is represented by the following Structural ~~Formula I~~ **Formula I (SEQ ID NO:199)**:



and pharmaceutically acceptable salts thereof, wherein

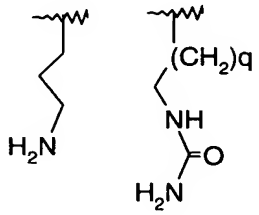
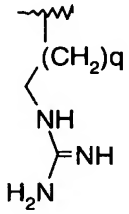
W is Glu, Gln, Asp, Asn, Ala, Gly, Thr, Ser, Pro, Met, Ile, Val, Arg, His, Tyr, Trp, Phe, Lys, Leu, Cya, or is absent;

R^1 is -H, $-C(O)CH_3$, $-C(O)(CH_2)_{1-4}CH_3$, $-C(O)(CH_2)_{1-4}NHC(NH)NH_2$, Tyr-βArg-, Ac-Tyr-β-hArg-, gluconoyl-Tyr-Arg-, Ac-diaminobutyryl-, Ac-diaminopropionyl-, N-propionyl-, N-butyryl-, N-valeryl-, N-methyl-Tyr-Arg-, N-glutaryl-Tyr-Arg-, N-succinyl-Tyr-Arg-, R^6-$SO_2NHC(O)CH_2CH_2C(O)$-, R^6-$SO_2NHC(O)CH_2CH_2C(O)$Arg-, R^6-$SO_2NHCH_2CH_2CH_2C(O)$-, C_3-C_7 cycloalkylcarbonyl, phenylsulfonyl, C_8-C_{14} bicyclic arylsulfonyl, phenyl-$(CH_2)_qC(O)$-, C_8-C_{14} bicyclic aryl-$(CH_2)_qC(O)$-,


,

,

,

, or

, wherein

R^2 is -H, -NH_2, -NHC(O)CH_3, -NHC(O)$(CH_2)_{1-4}CH_3$,
–NH-TyrC(O)CH_3, R^6SO_2NH-, Ac-Cya-NH-, Tyr-NH-,
HO-(C_6H_5)-$CH_2CH_2C(O)NH$-, or CH_3-(C_6H_5)-$C(O)CH_2CH_2C(O)NH$-;

R^3 is C_1-C_4 straight or branched alkyl, NH_2-CH_2-$(CH_2)_q$-, HO-CH_2-,
$(CH_3)_2CHNH(CH_2)_4$-, $R^6(CH_2)_q$-, R^6SO_2NH-, Ser, Ile,


or

;

q is 0, 1, 2, or 3;

R^6 is a phenyl or C_8-C_{14} bicyclic aryl;

m is 1 or 2;

n is 1, 2, 3, or 4;

R^9 is $(CH_2)_p$ or $(CH_3)_2C$-;

p is 1 or 2;

R^{10} is NH- or is absent;

R^7 is a 5- or 6-membered heteroaryl or a 5- or 6-membered heteroaryl ring optionally substituted with R^4;

R^4 is H, C_1-C_4 straight or branched alkyl, phenyl, benzyl, or
(C_6H_5)-CH_2-O-CH_2-;

R^8 is phenyl, a phenyl ring optionally substituted with X, or cyclohexyl;

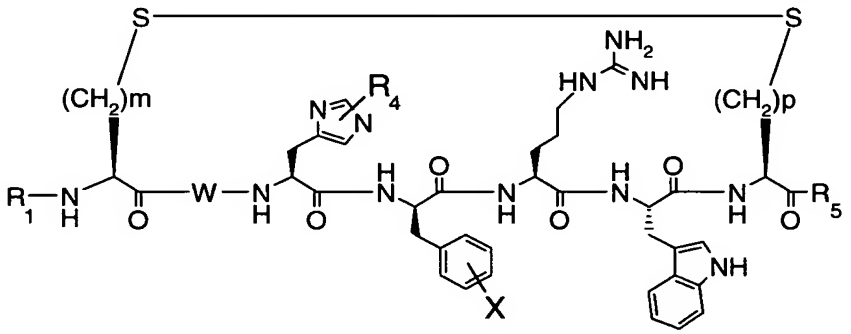
X is H, Cl, F, Br, methyl, or methoxy;

R^{11} is -C(O) or $-CH_2$;

R^5 is $-NH_2$, -OH, glycinol, NH_2-Pro-Ser-, NH_2-Pro-Lys-, HO-Ser-, HO-Pro-Ser-, HO-Lys-, -Ser alcohol, -Ser-Pro alcohol, -Lys-Pro alcohol, $HOCH_2CH_2$-O-CH_2CH_2NH-, NH_2-Phe-Arg-, NH_2-Glu-, $NH_2CH_2RCH_2NH$-, RHN-, or RO- where R is a C_1-C_4 straight or branched alkyl; and

L is –S-S- or –S-CH_2-S-.

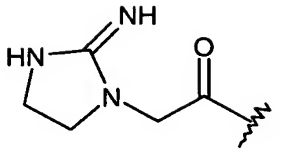
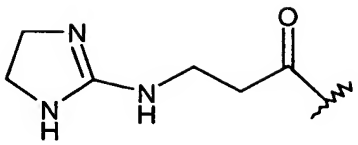
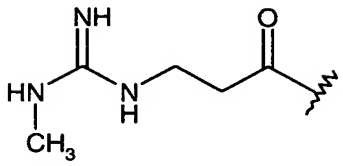
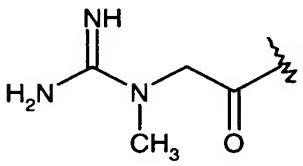
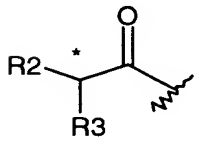
A preferred group of MC4R agonist peptides for use in the present invention includes compounds of Structural ~~Formula II~~ **Formula II (SEQ ID NO:200)**:



and pharmaceutically acceptable salts thereof, wherein

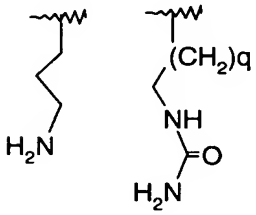
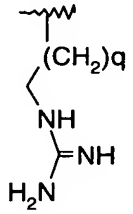
W is Glu, Gln, Asp, Asn, Ala, Gly, Thr, Ser, Pro, Met, Ile, Val, Arg, His, Tyr, Trp, Phe, Lys, Leu, Cya, or is absent;

R^1 is -H, $-C(O)CH_3$, $-C(O)(CH_2)_{1-4}CH_3$, $-C(O)(CH_2)_{1-4}NHC(NH)NH_2$, Tyr-βArg-, Ac-Tyr-β-hArg-, gluconoyl-Tyr-Arg-, Ac-diaminobutyryl-, Ac-diaminopropionyl-, N-propionyl-, N-butyryl-, N-valeryl-, N-methyl-Tyr-Arg-, N-glutaryl-Tyr-Arg-, N-succinyl-Tyr-Arg-, R^6-$SO_2NHC(O)CH_2CH_2C(O)$-, R^6-$SO_2NHC(O)CH_2CH_2C(O)$Arg-, R^6-$SO_2NHCH_2CH_2CH_2C(O)$-, C_3-C_7 cycloalkylcarbonyl, phenylsulfonyl, C_8-C_{14} bicyclic arylsulfonyl, phenyl-$(CH_2)_qC(O)$-, C_8-C_{14} bicyclic aryl-$(CH_2)_qC(O)$-,


,

,

,

, or

, wherein

R^2 is -H, -NH_2, -NHC(O)CH_3, -NHC(O)$(CH_2)_{1-4}CH_3$,
–NH-TyrC(O)CH_3, R^6SO_2NH-, Ac-Cya-NH-, Tyr-NH-,
HO-(C_6H_5)-CH_2CH_2C(O)NH-, or CH_3-(C_6H_5)-C(O)CH_2CH_2C(O)NH-;

R^3 is C_1-C_4 straight or branched alkyl, NH_2-CH_2-$(CH_2)_q$-, HO-CH_2-,
$(CH_3)_2CHNH(CH_2)_4$-, $R^6(CH_2)_q$-, R^6SO_2NH-, Ser, Ile,


or

;

q is 0, 1, 2, or 3;

R^6 is a phenyl or C_8-C_{14} bicyclic aryl;

m is 1 or 2;

p is 1 or 2;

R^4 is H, C_1-C_4 straight or branched alkyl, phenyl, benzyl, or
(C_6H_5)-CH_2-O-CH_2-;

X is H, Cl, F, Br, methyl, or methoxy; and

R^5 is -NH_2, -OH, glycinol, NH_2-Pro-Ser-, NH_2-Pro-Lys, HO-Ser-,
HO-Pro-Ser-, HO-Lys-, -Ser alcohol, -Ser-Pro alcohol, -Lys-Pro alcohol,
$HOCH_2CH_2$-O-CH_2CH_2NH-, NH_2-Phe-Arg-, NH_2-Glu-,

$NH_2CH_2RCH_2NH$-, RHN-, or RO- where R is a C_1-C_4 straight or branched alkyl.

Another preferred group of MC4R agonist peptides for use in the present invention are compounds of the Structural Formula II, wherein W is Glu or is absent; R_4 is H or CH_3; X is H, Cl, F, or Br; and R_5 is NH_2 or OH.

Yet another preferred group of MC4R agonist peptides are compounds of Structural Formula II wherein W is Glu or is absent; R^1 is H-, Ac-, Arg-, Ac-Arg-, or Ac-D-Arg-; m is 1 or 2; p is 1; and R^5 is NH_2 or OH.

A preferred compound for use in the present invention is an MC4R agonist peptide of Structural Formula II wherein W is absent; R^1 is Ac-; m is 2; p is 1; and R^5 is NH_2.

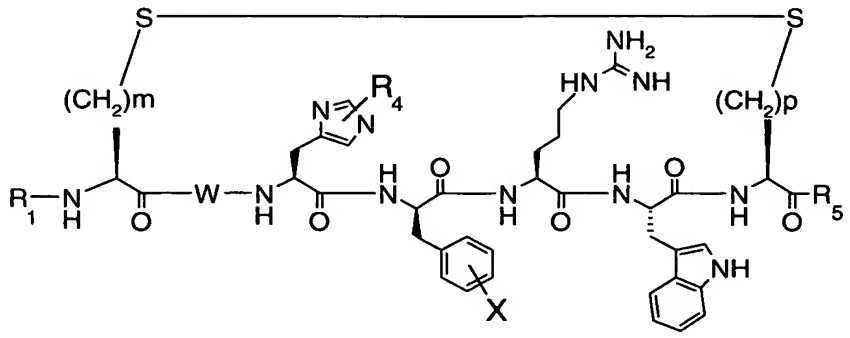
Another preferred compound for use in the present invention is an MC4R agonist peptide of Structural Formula II wherein W is Glu; R^1 is Ac-Arg-; m is 1; p is 1; and R^5 is NH_2.

Another preferred compound for use in the present invention is an MC4R agonist peptide of Structural Formula II wherein W is absent; R^1 is H; m is 2; p is 1; and R^5 is NH_2.

Another preferred compound for use in the present invention is an MC4R agonist peptide of Structural Formula II wherein W is absent; R^1 is Arg-; m is 2; p is 1; and R^5 is OH.

A most preferred compound for use in the present invention is an MC4R agonist peptide of Structural Formula II wherein W is Glu; R^1 is Ac-D-Arg-; m is 1; p is 1; and R^5 is NH_2.

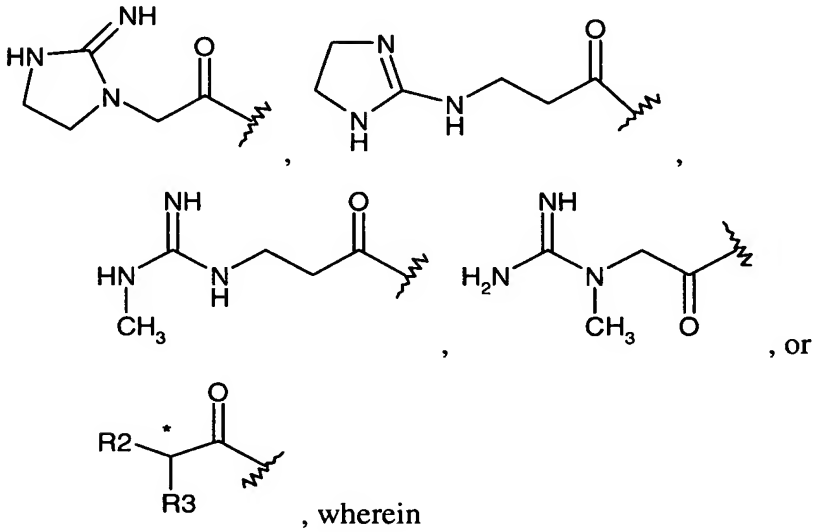
An alternative preferred group of MC4R agonist peptides for use in the present invention is represented by the following Structural ~~Formula III~~ **Formula III (SEQ ID NO:201)**:



and pharmaceutically acceptable salts thereof, wherein

W is a single bond, Glu, Gln, Asp, Asn, Ala, Gly, Thr, Ser, Pro, Met, Ile, Val, Arg, His, Tyr, Trp, or Phe;

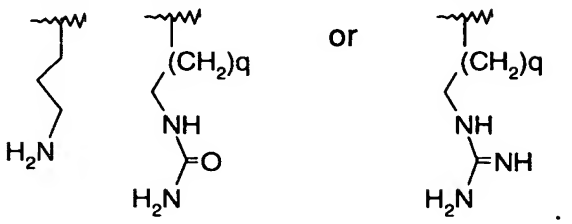
R_1 is -H, $-C(O)CH_3$, $-C(O)(CH_2)_{1-4}NH-C(NH)NH_2$, Tyr-βArg, gluconoyl-Tyr-Arg, Ac-Dab, Ac-Dap, N-succinyl-Tyr-Arg, N-propionyl, N-valeryl, N-glutaryl-Tyr-Arg, N-butyryl,



, wherein

R_2 is -H, $-NH_2$, $-NHC(O)CH_3$, $-NHC(O)(CH_2)_{1-4}CH_3$, Tyr, or -NH-Tyr-$C(O)CH_3$;

R_3 is C_1-C_4 straight or branched alkyl, Ser, Ile, Arg,



;

q is 0, 1, 2, or 3;

m is 1 or 2;

p is 1 or 2;

R_4 is -H, $-CH_3$, or $-(CH_2)_{1-3}CH_3$;

X is -H, -Cl, -F, -Br, methyl, or methoxy; and

R_5 is $-NH_2$, -OH, glycinol, -Ser-Pro-NH_2, -Lys-Pro-NH_2, -Ser-OH, -Ser-Pro-OH, -Lys-Pro-OH, -Arg-Phe-NH_2, -Glu-NH_2, -NHR, or -OR, where R is $-CH_3$ or $-(CH_2)_{1-3}CH_3$.

MC4R agonist peptides for use in the present invention include, but are not limited to, those compounds listed in the following table:

Table 1. Specific compounds within the present invention.

No.	Name
1	Ac-cyclo[Cys-His-D-Phe-Arg-Trp-Cys]-NH_2
2	Ac-Cya-Arg-cyclo[Cys-Ala-His-D-Phe-Arg-Trp-Cys]-NH_2
3	Ac-Tyr-Arg-cyclo[Cys-Ala-His-D-Phe-Arg-Trp-Cys]-NH_2
4	Ac-Tyr-Arg-cyclo[Cys-Arg-His-D-Phe-Arg-Trp-Cys]-NH_2
5	Ac-Tyr-Arg-cyclo[Cys-Asn-His-D-Phe-Arg-Trp-Cys]-NH_2
6	Ac-cyclo[Cys-Asp-His-D-Phe-Arg-Trp-Cys]-NH_2
7	Ac-Tyr-Arg-cyclo[Cys-Asp-His-D-Phe-Arg-Trp-Cys]-NH_2
8	Ac-cyclo[Cys-Gln-His-D-Phe-Arg-Trp-Cys]-NH_2
9	Ac-Tyr-Arg-cyclo[Cys-Gln-His-D-Phe-Arg-Trp-Cys]-OH
10	Ac-Tyr-Arg-cyclo[Cys-Gln-His-D-Phe-Arg-Trp-Cys]-OMe
11	Tyr-Arg-cyclo[Cys-Gly-His-D-Phe-Arg-Trp-Cys]-NH_2
12	Ac-Tyr-Arg-cyclo[Cys-Gly-His-D-Phe-Arg-Trp-Cys]-NH_2
13	Ac-Tyr-Arg-cyclo[Cys-His-His-D-Phe-Arg-Trp-Cys]-NH_2
14	Ac-Tyr-Arg-cyclo[Cys-Ile-His-D-Phe-Arg-Trp-Cys]-NH_2
15	Ac-cyclo[Cys-Leu-His-D-Phe-Arg-Trp-Cys]-NH_2
16	Ac-cyclo[Cys-Lys-His-D-Phe-Arg-Trp-Cys]-NH_2
17	N-methyl-Tyr-Arg-cyclo[Cys-Met-His-D-Phe-Arg-Trp-Cys]-NH_2
18	Ac-Tyr-Arg-cyclo[Cys-Met-His-D-Phe-Arg-Trp-Cys]-NH_2
19	Ac-Tyr-Arg-cyclo[Cys-Phe-His-D-Phe-Arg-Trp-Cys]-NH_2

No.	Name
20	Ac-Tyr-Arg-cyclo[Cys-Pro-His-D-Phe-Arg-Trp-Cys]-NH_2
21	Ac-Tyr-Arg-cyclo[Cys-Ser-His-D-Phe-Arg-Trp-Cys]-NH_2
22	Ac-Tyr-Arg-cyclo[Cys-Thr-His-D-Phe-Arg-Trp-Cys]-NH_2
23	Ac-Tyr-Arg-cyclo[Cys-Trp-His-D-Phe-Arg-Trp-Cys]-NH_2
24	Ac-Tyr-Arg-cyclo[Cys-Tyr-His-D-Phe-Arg-Trp-Cys]-NH_2
25	Ac-Tyr-Arg-cyclo[Cys-Val-His-D-Phe-Arg-Trp-Cys]-NH_2
26	Ac-Arg-cyclo[Cys-Cya-His-D-Phe-Arg-Trp-Cys]-NH_2
27	Ac-D-Arg-cyclo[Cys-Cya-His-D-Phe-Arg-Trp-Cys]-NH_2
28	Ac-Tyr-Arg-cyclo[Cys-Cya-His-D-Phe-Arg-Trp-Cys]-NH_2
29	cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-NH_2
30	Ac-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-NH_2
31	Ac-cyclo[Cys-Glu-His-(4-F-D-Phe)-Arg-Trp-Cys]-NH_2
32	Ac-cyclo[Cys-Glu-His-(4-Cl-D-Phe)-Arg-Trp-Cys]-NH_2
33	Ac-cyclo[Cys-Glu-His-(4-Br-D-Phe)-Arg-Trp-Cys]-NH_2
34	Ac-cyclo[Cys-Glu-(1-Me-His)-D-Phe-Arg-Trp-Cys]-NH_2
35	Ac-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-Lys-Pro-NH_2
36	Ac-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-Ser-Pro-NH_2
37	N-propionyl-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-NH_2
38	N-butyryl-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-NH_2
39	N-valeryl-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-NH_2
40	3-guanidinopropionyl-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-NH_2
41	4-guanidinobutyryl-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-NH_2
42	5-guanidinovaleryl-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-NH_2
43	Ac-diaminopropionyl-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-NH_2
44	Ac-diaminobutyryl-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-NH_2
45	Arg-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-OH
46	D-Arg-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-NH_2
47	Ac-D-Arg-cyclo[Cys-Glu-His-Phe-Arg-Trp-Cys]-NH_2
48	Ac-Arg-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-NH_2
49	Ac-Arg-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-OH
50	Ac-Arg-cyclo[Cys-Glu-His-(4-Cl-D-Phe)-Arg-Trp-Cys]-NH_2
51	Ac-Arg-cyclo[Cys-Glu-(1-Me-His)-D-Phe-Arg-Trp-Cys]-NH_2
52	Ac-D-Arg-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-NH_2
53	Ac-D-Arg-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-OH
54	Ac-hArg-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-NH_2
55	Ac-Cit-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-NH_2
56	Ac-Cit-cyclo[Cys-Glu-(1-Me-His)-D-Phe-Arg-Trp-Cys]-NH_2
57	Ac-Leu-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-NH_2
58	Ac-Lys-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-NH_2
59	Ac-Lys(ipr)-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-NH_2
60	Ac-nLeu-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-NH_2
61	Ac-nLeu-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-Ser-Pro-NH_2
62	Ac-Orn-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-NH_2
63	Ac-Val-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-NH_2
64	N-(2-naphthalenesulfonyl)-D-Arg-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-NH_2
65	N-(2-naphthalenesulfonylamino-4-oxo-butyryl)-D-Arg-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-NH_2
66	3-(4-hydroxyphenyl)propionyl-Arg-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-NH_2

No.	Name
67	3-(4-methylbenzoyl)propionyl-Arg-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-NH_2
68	Tyr-Arg-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-NH_2
69	Tyr-Arg-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-OH
70	Tyr-Arg-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-NH-$(CH_2)_6$-NH_2
71	Tyr-Arg-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-Glu-NH_2
72	Ac-Tyr-Arg-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-NH_2
73	Ac-Tyr-Arg-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-OH
74	N-succinyl-Tyr-Arg-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-NH_2
75	N-glutaryl-Tyr-Arg-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-NH_2
76	N-glutaryl-Tyr-Arg-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-OH
77	gluconoyl-Tyr-Arg-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-NH_2
78	Ac-Tyr-Arg-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys] alcohol
79	Ac-Tyr-D-Arg-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-NH_2
80	Ac-Tyr-Arg-cyclo[D-Cys-Glu-His-D-Phe-Arg-Trp-Cys]-NH_2
81	Ac-Tyr-Arg-cyclo[Cys-Glu-(1-Me-His)-D-Phe-Arg-Trp-Cys]-NH_2
82	Ac-Tyr-Arg-cyclo[Cys-Glu-(1-Me-D-His)-D-Phe-Arg-Trp-Cys]-NH_2
83	Ac-Tyr-Arg-cyclo[Cys-Glu-His-(4-F-D-Phe)-Arg-Trp-Cys]-NH_2
84	Ac-Tyr-Arg-cyclo[Cys-Glu-(1-Me-His)-(4-F-D-Phe)-Arg-Trp-Cys]-NH_2
85	Ac-Tyr-Arg-cyclo[Cys-Glu-(1-Me-D-His)-(4-F-D-Phe)-Arg-Trp-Cys]-NH_2
86	Ac-Tyr-Arg-cyclo[Cys-Glu-His-(4-Cl-D-Phe)-Arg-Trp-Cys]-NH_2
87	Ac-Arg-cyclo[Cys-Glu-(1-Me-His)-(4-Cl-D-Phe)-Arg-Trp-Cys]-NH_2
88	Ac-Tyr-Arg-cyclo[Cys-Glu-(1-Me-D-His)-(4-Cl-D-Phe)-Arg-Trp-Cys]-NH_2
89	Ac-Tyr-Arg-cyclo[Cys-Glu-His-(4-Br-D-Phe)-Arg-Trp-Cys]-NH_2
90	Ac-Tyr-Arg-cyclo[Cys-Glu-(1-Me-His)-(4-Br-D-Phe)-Arg-Trp-Cys]-NH_2
91	Ac-Tyr-Arg-cyclo[Cys-Glu-(1-Me-D-His)-(4-Br-D-Phe)-Arg-Trp-Cys]-NH_2
92	Ac-Tyr-Arg-cyclo[Cys-Glu-His-(4-Me-D-Phe)-Arg-Trp-Cys]-NH_2
93	Ac-Tyr-Arg-cyclo[Cys-Glu-His-(4-OMe-D-Phe)-Arg-Trp-Cys]-NH_2
94	Ac-Tyr-Arg-cyclo[Cys-Glu-(1-Me-His)-(4-OMe-D-Phe)-Arg-Trp-Cys]-NH_2
95	Ac-Tyr-Arg-cyclo[Cys-Glu-(1-Me-D-His)-(4-OMe-D-Phe)-Arg-Trp-Cys]-NH_2
96	Ac-Tyr-Arg-cyclo[Cys-Glu-(3-Me-His)-D-Phe-Arg-Trp-Cys]-NH_2
97	Ac-Tyr-Arg-cyclo[Cys-Glu-(5-Me-His)-D-Phe-Arg-Trp-Cys]-NH_2
98	Ac-Tyr-Arg-cyclo[Cys-Glu-(5-Me-D-His)-D-Phe-Arg-Trp-Cys]-NH_2
99	Ac-Tyr-Arg-cyclo[Cys-Glu-(1-benzyl-His)-D-Phe-Arg-Trp-Cys]-NH_2
100	Ac-Tyr-Arg-cyclo[Cys-Glu-(1-benzyl-D-His)-D-Phe-Arg-Trp-Cys]-NH_2
101	Ac-Tyr-Arg-cyclo[Cys-Glu-(1-Bom-His)-D-Phe-Arg-Trp-Cys]-NH_2
102	Ac-Tyr-Arg-cyclo[Cys-Glu-(1-pyrazolyl-Ala)-D-Phe-Arg-Trp-Cys]-NH_2
103	Ac-Tyr-Arg-cyclo[Cys-Glu-(4-phenyl-1H-imidazol-2-yl-Ala)-D-Phe-Arg-Trp-Cys]-NH_2
104	Ac-Tyr-Arg-cyclo[Cys-Glu-(4-phenyl-1H-imidazol-2-yl-D-Ala)-D-Phe-Arg-Trp-Cys]-NH_2
105	Ac-Tyr-Arg-cyclo[Cys-Glu-(2-pyrazine-Ala)-D-Phe-Arg-Trp-Cys]-NH_2
106	Ac-Tyr-Arg-cyclo[Cys-Glu-(ß-(1,2,4-triazol-3-yl))-Ala)-D-Phe-Arg-Trp-Cys]-NH_2
107	Ac-Tyr-Arg-cyclo[Cys-Glu-(ß-(1,2,4-triazol-3-yl))-D-Ala)-D-Phe-Arg-Trp-Cys]-NH_2
108	Ac-Tyr-Arg-cyclo[Cys-Glu-(ß-((1-benzyl)-1,2,4-triazol-3-yl))-Ala)-D-Phe-Arg-Trp-Cys]-NH_2
109	Ac-Tyr-Arg-cyclo[Cys-Glu-(ß-((1-benzyl)-1,2,4-triazol-3-yl))-D-Ala)-D-Phe-Arg-Trp-Cys]-NH_2
110	Ac-Tyr-Arg-cyclo[Cys-Glu-(ß-(2-furyl)-Ala)-D-Phe-Arg-Trp-Cys]-NH_2
111	Ac-Tyr-Arg-cyclo[Cys-Glu-(ß-(thien-2-yl)-Ala)-D-Phe-Arg-Trp-Cys]-NH_2
112	Ac-Tyr-Arg-cyclo[Cys-Glu-(ß-(1,3-thiazol-4-yl)-Ala)-D-Phe-Arg-Trp-Cys]-NH_2
113	Ac-Tyr-Arg-cyclo[Cys-Glu-(ß-(pyridin-4-yl)-Ala)-D-Phe-Arg-Trp-Cys]-NH_2
114	Ac-Tyr-Arg-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-glycinol

No.	Name
115	Ac-Tyr-Arg-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-2-(2-aminoethoxy)ethanol
116	Ac-Tyr-Arg-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-Ser alcohol
117	Ac-Tyr-Arg-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-NH-$(CH_2)_6$-NH_2
118	Ac-Tyr-Arg-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-Glu-NH_2
119	Ac-Tyr-Arg-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-Ser-Pro-NH_2
120	Ac-Tyr-Arg-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-Ser-Pro alcohol
121	Ac-Tyr-Arg-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-Lys-Pro-NH_2
122	Ac-Tyr-Arg-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-Lys-Pro alcohol
123	Ac-Tyr-Arg-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-Arg-Phe-NH_2
124	Ac-Tyr-Cit-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-NH_2
125	Ac-Tyr-Cit-cyclo[Cys-Glu-(1-Me-His)-D-Phe-Arg-Trp-Cys]-NH_2
126	Ac-Tyr-hArg-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-NH_2
127	Ac-Tyr-(1-β-hArg)-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-NH_2
128	Ac-Tyr-Lys-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-NH_2
129	Ac-Tyr-Ser-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-NH_2
130	Ac-Tyr-Val-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-NH_2
131	N-succinyl-Tyr-Arg-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-OH
132	cyclo[hCys-His-D-Phe-Arg-Trp-Cys]-NH_2
133	cyclo[hCys-His-D-Phe-Arg-Trp-Cys]-OH
134	cyclo[hCys-His-(4-F-D-Phe)-Arg-Trp-Cys]-NH_2
135	cyclo[hCys-His-(4-Cl-D-Phe)-Arg-Trp-Cys]-NH_2
136	Ac-cyclo[hCys-His-Phe-Arg-Trp-Cys]-NH_2
137	Ac-cyclo[hCys-His-D-Phe-Arg-Trp-Cys]-NH_2
138	Ac-cyclo[hCys-His-D-Phe-Arg-Trp-Cys]-OH
139	Ac-cyclo[hCys-His-(4-F-D-Phe)-Arg-Trp-Cys]-NH_2
140	Ac-cyclo[hCys-His-(4-Cl-D-Phe)-Arg-Trp-Cys]-NH_2
141	N-cyclopropanecarbonyl-cyclo[hCys-His-D-Phe-Arg-Trp-Cys]-NH_2
142	N-cyclobutanecarbonyl-cyclo[hCys-His-D-Phe-Arg-Trp-Cys]-NH_2
143	N-cyclopentanecarbonyl-cyclo[hCys-His-D-Phe-Arg-Trp-Cys]-NH_2
144	N-cyclohexanecarbonyl-cyclo[hCys-His-D-Phe-Arg-Trp-Cys]-NH_2
145	N-hexanoyl-cyclo[hCys-His-D-Phe-Arg-Trp-Cys]-NH_2
146	N-benzoyl-cyclo[hCys-His-D-Phe-Arg-Trp-Cys]-NH_2
147	4-phenylbutyryl-cyclo[hCys-His-D-Phe-Arg-Trp-Cys]-NH_2
148	3-guanidinopropionyl-cyclo[hCys-His-D-Phe-Arg-Trp-Cys]-NH_2
149	5-guanidinovaleryl-cyclo[hCys-His-D-Phe-Arg-Trp-Cys]-NH_2
150	N-phenylsulfonyl-cyclo[hCys-His-D-Phe-Arg-Trp-Cys]-NH_2
151	N-(2-naphthalenesulfonyl)-cyclo[hCys-His-D-Phe-Arg-Trp-Cys]-NH_2
152	N-(4-phenylsulfonamido-4-oxo-butyryl)-cyclo[hCys-His-D-Phe-Arg-Trp-Cys]-NH_2
153	Arg-cyclo[hCys-His-D-Phe-Arg-Trp-Cys]-NH_2
154	D-Arg-cyclo[hCys-His-D-Phe-Arg-Trp-Cys]-NH_2
155	Arg-cyclo[hCys-His-D-Phe-Arg-Trp-Cys]-OH
156	Arg-cyclo[hCys-(1-Me-His)-D-Phe-Arg-Trp-Cys]-NH_2
157	Arg-cyclo[hCys-(1-Me-D-His)-D-Phe-Arg-Trp-Cys]-NH_2
158	Ac-Arg-cyclo[hCys-His-D-Phe-Arg-Trp-Cys]-NH_2
159	~~Ac-Arg-cyclo[hCys-His-D-Phe-Arg-Trp-Cys]-NH_2~~ **Ac-Arg-cyclo[hCys-His-D-Phe-Arg-Trp-Cys]-OH**
160	Ac-nLeu-cyclo[hCys-His-D-Phe-Arg-Trp-Cys]-NH_2
161	phenylsulfonyl-Gly-cyclo[hCys-His-D-Phe-Arg-Trp-Cys]-NH_2

No.	Name
162	Tyr-Arg-cyclo[hCys-His-D-Phe-Arg-Trp-Cys]-NH_2
163	Tyr-Arg-cyclo[hCys-His-D-Phe-Arg-Trp-Cys]-OH
164	Ac-Tyr-Arg-cyclo[hCys-His-D-Phe-Arg-Trp-Cys]-NH_2
165	Ac-Tyr-Arg-cyclo[hCys-His-D-Phe-Arg-Trp-Cys]-OH
166	Ac-Tyr-Arg-cyclo[hCys-Glu-His-D-Phe-Arg-Trp-Cys]-NH_2
167	Ac-cyclo[hCys-His-(ß-cyclohexyl-D-Ala)-Arg-Trp-Cys]-NH_2
168	Ac-cyclo[hCys-His-D-Phe-Arg-Trp-penicillamine]-NH_2
169	Ac-cyclo[hCys-His-(4-Cl-D-Phe)-Arg-Trp-penicillamine]-NH_2
170	N-hexanoyl-cyclo[hCys-His-D-Phe-Arg-Trp-penicillamine]-NH_2
171	N-cyclopentanecarbonyl-cyclo[hCys-His-D-Phe-Arg-Trp-penicillamine]-NH_2
172	N-cyclohexanecarbonyl-cyclo[hCys-His-D-Phe-Arg-Trp-penicillamine]-NH_2
173	N-benzoyl-cyclo[hCys-His-D-Phe-Arg-Trp-penicillamine]-NH_2
174	4-phenylbutyryl-cyclo[hCys-His-D-Phe-Arg-Trp-penicillamine]-NH_2
175	N-phenylsulfonyl-cyclo[hCys-His-D-Phe-Arg-Trp-penicillamine]-NH_2
176	(4-benzenesulfonamide)butyryl-cyclo[hCys-His-D-Phe-Arg-Trp-penicillamine]-NH_2
177	Ac-nLeu-cyclo[hCys-His-D-Phe-Arg-Trp-penicillamine]-NH_2
178	N-phenylsulfonyl-Gly-cyclo[hCys-His-D-Phe-Arg-Trp-penicillamine]-NH_2
179	cyclo[3-thiopropionyl-His-D-Phe-Arg-Trp-hCys]-NH_2
180	cyclo[Cys-His-D-Phe-Arg-Trp-hCys]-NH_2
181	cyclo[Cys-His-(4-F-D-Phe)-Arg-Trp-hCys]-NH_2
182	cyclo[Cys-His-(4-Cl-D-Phe)-Arg-Trp-hCys]-NH_2
183	Ac-cyclo[Cys-His-D-Phe-Arg-Trp-hCys]-NH_2
184	Ac-cyclo[Cys-His-(4-F-D-Phe)-Arg-Trp-hCys]-NH_2
185	Ac-cyclo[Cys-His-(4-Cl-D-Phe)-Arg-Trp-hCys]-NH_2
186	Arg-cyclo[Cys-His-D-Phe-Arg-Trp-hCys]-NH_2
187	Arg-cyclo[Cys-His-(4-F-D-Phe)-Arg-Trp-hCys]-NH_2
188	Arg-cyclo[Cys-His-(4-Cl-D-Phe)-Arg-Trp-hCys]-NH_2
189	Ac-Arg-cyclo[Cys-His-D-Phe-Arg-Trp-hCys]-NH_2
190	Ac-Arg-cyclo[Cys-His-(4-F-D-Phe)-Arg-Trp-hCys]-NH_2
191	Ac-Arg-cyclo[Cys-His-(4-Cl-D-Phe)-Arg-Trp-hCys]-NH_2
192	Ac-Tyr-Arg-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-hCys]-NH_2
193	Ac-cyclo[hCys-His-D-Phe-Arg-Trp-hCys]-NH_2
194	Arg-cyclo[hCys-His-D-Phe-Arg-Trp-hCys]-NH_2
195	Ac-Arg-cyclo[hCys-His-D-Phe-Arg-Trp-hCys]-NH_2
196	Ac-Tyr-Arg-cyclo[hCys-His-D-Phe-Arg-Trp-hCys]-NH_2
197	Ac-Tyr-Arg-cyclo[hCys-Glu-His-D-Phe-Arg-Trp-hCys]-NH_2
198	Ac-cyclo(S-CH_2-S)[Cys-His-D-Phe-Arg-Trp-Cys]-NH_2

A preferred group for use in the invention includes MC4R agonist peptides having Compound Nos. 48, 52, 132, 137, and 155. More preferred is a group consisting of Compound Numbers 52 and 137. A more preferred compound for use in the present invention is Compound Number 137, denoted by the name Ac-cyclo[hCys-His-D-Phe-Arg-Trp-Cys]-NH_2, as the MC4R agonist peptide. A most preferred compound for use in the present invention is Compound Number 52, denoted by the name Ac-D-Arg-cyclo[Cys-Glu-His-D-Phe-Arg-Trp-Cys]-NH_2, as the MC4R agonist peptide.

As used herein, "C_1-C_4 straight or branched alkyl" means a straight chained or branched hydrocarbon having 1 to 4 carbon atoms, which is completely saturated and unsubstituted. "C_3-C_7 cycloalkyl" refers to a saturated, unsubstituted hydrocarbon ring having 3 to 7 carbon atoms. A "C_1-C_4 straight or branched heteroalkyl" refers to a straight chained or branched hydrocarbon having 1 to 4 carbon atoms, which is completely saturated and unsubstituted, that also contains at least one "heteroatom." A "heteroatom" is nitrogen, oxygen, or sulfur. "C_3-C_7 heterocycloalkyl" refers to a saturated, unsubstituted hydrocarbon ring having 3 to 7 carbon atoms, which also contains at least one "heteroatom." C_1-C_4 straight or branched alkyl, C_3-C_7 cycloalkyl, C_1-C_4 straight or branched heteroalkyl, and C_3-C_7 heterocycloalkyl may be used as generic modifiers to describe a genus of substituents on another functional group such as a carbonyl, sulfonyl, or sulfonamide. For example, a "C_3-C_7 cycloalkylcarbonyl" refers to a genus of saturated, unsubstituted hydrocarbon rings having 3 to 7 carbon atoms that are bonded to a carbonyl group.

A "C_8-C_{14} bicyclic aryl" refers to two or three hydrocarbon rings fused together, having 8 to 14 carbon atoms, such as naphthalene. A C_8-C_{14} bicyclic aryl ring system has at least one aromatic ring. A "5- or 6-membered heteroaryl" refers to a monocyclic aromatic ring having 5 or 6 atoms, of which 1-4 atoms are heteroatoms. An "8- to 14-membered bicyclic heteroaryl" ring refers to two or three hydrocarbon rings fused together, having 8 to 14 atoms, at least one aromatic ring, and 1-4 heteroatoms.

A phenyl, benzyl, benzoyl, C_8-C_{14} bicyclic aryl, 5- or 6-membered heteroaryl, or 8- to 14-membered bicyclic heteroaryl may be unsubstituted or substituted with C_1-C_4 straight or branched alkyl, F, Cl, Br, –OH, methoxy, phenyl, benzyl, benzoyl, or benzyloxymethyl. Furthermore, phenyl, benzyl, benzoyl, C_8-C_{14} bicyclic aryl, 5- or 6-membered heteroaryl, and 8- to 14-membered bicyclic heteroaryl may be used as generic modifiers to describe a genus of substituents on another functional group such as a carbonyl, sulfonyl, or sulfonamide. For example, a "C_8-C_{14} bicyclic arylsulfonyl" refers to a genus of bicyclic aryl rings having 8 to 14 carbon atoms that are bonded to a sulfonyl group.

Modified amino acids are indicated by parentheses around the amino acid and the modification thereto (*e.g.*, (4-Cl-D-Phe) is a 4-chloro modification on the D-isomer of phenylalanine). With respect to moieties depicted in Structural Formula I, Structural

Formula II, and Structural Formula III, the single letter designations are as defined and do not refer to single letter amino acids corresponding to those letters.

The letter "D" preceding the above-mentioned 3-letter abbreviations, *e.g.*, "D-Phe," means the D-form of the amino acid. When the single letter abbreviation is used for an amino acid, a "d" will precede the letter to designate the D-form of the amino acid (*e.g.*, dF = D-Phe).

An "amino alcohol" is an amino acid that has been modified by reducing the carbonyl group of the C-terminus to a ~~methyl~~ **methylene** group. Amino alcohols are denoted by the general nomenclature "Xaa alcohol," wherein Xaa is the specific amino acid from which the carbonyl group has been removed. To illustrate, "Ser alcohol" has the structure H_2N-CH(CH_2OH)-CH_2OH as opposed to the Ser amino acid structure of H_2N-CH(CH_2OH)-COOH.

"Single bond," as used herein, refers to a structure that does not contain an amino acid at the specified position. It is used to signify that an amino acid is absent from that position such that the carbonyl adjacent to that position on one side and the amine adjacent to that position on the other side form a peptide bond with each other.

"*" means that both the D- and L- isomers are possible.

"Ac" refers to acetyl (*i.e.*, -C(O)CH_3).

"Orn" refers to ornithine.

"hCys" refers to homocysteine.

"hArg" refers to homoarginine.

"Lys(ipr)" refers to lysine(N-isopropyl).

"Cit" refers to citrulline.

"nLeu" refers to norleucine.

"Me" refers to methyl.

"OMe" refers to methoxy.

"Cya" refers to cysteic acid.

"Dap" refers to diaminopropionyl.

"Dab" refers to diaminobutyryl.

"Pharmaceutically-acceptable salt" refers to salts of the compounds of the Structural Formula I, Structural Formula II, or Structural Formula III that are substantially non-toxic to mammals. Typical pharmaceutically acceptable salts include those salts

prepared by reaction of the compounds of the present invention with a mineral or organic acid or an organic or inorganic base. Such salts are known as acid addition and base addition salts, respectively. It should be recognized that the particular counterion forming a part of any salt of this invention is not of a critical nature, so long as the salt as a whole is pharmaceutically acceptable and as long as the counterion does not contribute undesired qualities to the salt as a whole.

A pharmaceutical "acid addition salt" is a salt formed by reaction of the free base form of a compound of formula I with a pharmaceutical acid, such as described in the Encyclopedia of Pharmaceutical Technology, editors James Swarbrick and James C. Boylan, Vol. 13 (1996), "Preservation of Pharmaceutical Products to Salt Forms of Drugs and Absorption." Specific salt forms include, but are not limited to the: acetate, benzoate, benzenesulfonate, 4-chlorobenzenesulfonate; citrate; ethanesulfonate; fumarate; d-gluconate; d-glucuronate; glutarate; glycolate; hippurate; hydrochloride; 2-hydroxyethanesulfonate; dl-lactate; maleate; d-malate; l-malate; malonate; d-mandelate; l-mandelate; methanesulfonate; 1,5-napthalenedisulfonate; 2-naphthalenesulfonate; phosphate; salicylate; succinate; sulfate; d-tartrate; l-tartrate; and p-toluenesulfonate.

A pharmaceutical "base addition salt" is a salt formed by reaction of the free acid form of a compound of formula I with a pharmaceutical base, such as described in the Encyclopedia of Pharmaceutical Technology, *supra*. Specific salt forms include, but are not limited to the: calcium, diethanolamine, diethylamine, ethylenediamine, lysine, magnesium, piperazine, potassium, sodium, and tromethamine (Tris, Trizma) salts.

The term "active ingredient" means the MC4R agonist peptides generically described by Structural Formula I, Structural Formula II, and Structural Formula III, as well as the salts of such compounds.

The term "pharmaceutically acceptable" means that the carrier, diluent, excipients, and salt must be compatible with the other ingredients of the composition and not clinically deleterious to the recipient thereof. Pharmaceutical compositions of the present invention are prepared by procedures known in the art using well-known and readily available ingredients.

The term "agonist" includes any molecule that has affinity for the MC4 receptor, producing a measurable biological activity associated with weight loss in cells, tissues and organisms containing the MC4 receptor. In a similar manner, an "inverse agonist"

includes any molecule that has affinity for the MC4 receptor, producing a decreased intrinsic activity of the cell containing the MC4 receptor and is associated with weight gain in cells, tissues, and organisms containing the MC4 receptor. The term "antagonist" includes any molecule that partially or fully blocks, inhibits, or neutralizes a biological activity of the MC4 receptor. Assays measuring such activities are well known in the art.

The term "weight loss" includes any decrease in the mass of a patient. Weight loss may include overall loss of mass by the patient or, alternatively, loss of fat mass by the patient.

The term "obesity," also called corpulence or fatness, is the excessive accumulation of body fat, usually caused by the consumption of more calories than the body uses. The excess calories are then stored as fat, or adipose tissue. Overweight, if moderate, is not necessarily obesity, particularly in muscular or large-boned individuals. In general, however, a body weight twenty percent or more over the optimum tends to be associated with obesity.

A "subject" or "patient" is a mammal, preferably a human. Nonetheless, other mammals may be subjects or patients, including companion animals such as dogs and cats, laboratory animals such as rats, mice, monkeys, and guinea pigs, and farm animals such as cows, sheep, pigs, and horses.

The term "a patient in need thereof" is a patient either suffering from the claimed pathological condition or sequela thereof or is a patient at a recognized risk thereof as determined by medical diagnosis, *i.e.*, as determined by the attending physician.

The terms "treating," "treatment," and "therapy" as used herein refer to the management and care of a patient for the purpose of combating the disease, condition, or disorder. Treating includes the administration of an MC4R agonist peptide to prevent the onset of the symptoms or complications, alleviating the symptoms or complications, or eliminating the disease, condition, or disorder. Treating obesity therefore includes the inhibition of food intake, the inhibition of weight gain, and inducing weight loss in patients in need thereof.

Treatment may include curative therapy, prophylactic therapy, and preventive therapy. An example of "preventive therapy" is the prevention or lessened targeted pathological condition or disorder. Those in need of treatment include those already with

the disorder as well as those prone to have the disorder or those in whom the disorder is to be prevented.

A "therapeutically-effective amount" is the minimal amount of MC4R agonist peptide necessary to induce weight loss. An "effective amount" of the peptide administered to a subject will also depend on the type and severity of the disease or condition and on the characteristics of the subject, such as general health, age, sex, body weight and tolerance to drugs. The recipient patient's physician should determine the therapeutic dose administered in light of the relevant circumstances.

A therapeutically-effective amount can be administered prophylactically to a patient thought to be susceptible to development of a disease or condition. Such amount, when administered prophylactically to a patient, can also be effective to prevent or lessen the severity of the mediated condition. The dosage regimen utilizing the compounds of the present invention is selected by one of ordinary skill in the medical or veterinary arts, in view of a variety of factors, including, without limitation, the route of administration, the prior medical history of the recipient, the pathological condition or symptom being treated, the severity of the condition/symptom being treated, and the age and sex of the recipient patient. However, it will be understood that the therapeutic dose administered will be determined by the attending physician in the light of the relevant circumstances.

Generally, an effective minimum daily dose of a compound of the present invention will exceed about 0.01 mg. Typically, an effective maximum daily dose will not exceed about 1000 mg. More preferably, an effective minimum daily dose will be between about 0.05 mg and 50 mg, more preferably between 0.1 mg and 10 mg. Most preferably, an effective minimum daily dose of an MC4R agonist peptide in the present invention will exceed about 2 μg/kg and will not exceed about 20 μg/kg. The exact dose may be determined, in accordance with the standard practice in the medical arts of "dose titrating" the recipient; that is, initially administering a low dose of the compound, and gradually increasing the does until the desired therapeutic effect is observed. The desired dose may be presented in a single dose or as divided doses administered at appropriate intervals.

The peptides used in the invention may be chemically synthesized. Such methods for synthesis are well known in the art.

Example 1: Comparison of Continuous Infusion of MC4R Agonist Peptide Versus Daily Subcutaneous Injection

For this type of experiment, two solutions are prepared. First, a 5% dextrose solution is prepared by diluting 5 mL 50% dextrose solution (Biomeda) in 45 mL of sterile water for injection. This dextrose solution is subsequently referred to as "vehicle." Second, a stock solution of the MC4R agonist peptide ("P1") to be administered subcutaneously is prepared by dissolving 1.75 mg of P1 in 2 mL of the vehicle. This stock solution is then diluted to 0.088 mg/mL using that vehicle. This solution is subsequently referred to as P1sc solution. Both the P1sc solution and the vehicle are prepared fresh every three days and stored at 4°C in a sterile capped vial throughout the experiment. A separate solution of MC4R agonist peptide is prepared for continuous infusion using osmotic pumps by dissolving 11.1 mg of P1 in 3 mL of vehicle [3.7 mg/mL]. This solution is subsequently referred to as P1p solution. Ten ALZET® mini-osmotic pumps (implantable infusion pumps that continuously deliver materials to laboratory animals; Model 2002, 14-day payout at 0.5 μL/hour) are loaded using aseptic technique with either 200 μL P1p (n=5) or vehicle (n=5) solution and allowed to prime overnight in sterile 0.9% saline at 37°C in preparation for implantation into rats.

Twenty rats are selected for this experiment. Ten rats are anaesthetized briefly with isoflorane (3%, Abbott Laboratories). Each anaesthetized rat is implanted with an ALZET® pump using sterile technique. The rats are divided into four groups of five rats: two groups containing pumps and two groups with no pumps. Experimental samples are administered to the rats as follows:

Table 1. Administration scheme for a P1 study.

Group	Substance	Delivery method	Approximate daily dose (μg/kg active)
1	MC4-R peptide P1	Sustained release via pump	44
2	Vehicle	Sustained release via pump	0
3	MC4-R peptide P1	Daily subcutaneous injection	44
4	Vehicle	Daily subcutaneous injection	0

Each rat is weighed initially, and measurements of body composition are made for each animal using QNMR (quantitative nuclear magnetic resonance). Body mass is measured daily for fourteen days, and the cumulative change in body mass is calculated. Body composition is measured again at the end of the study.

Using a procedure such as that described above, results shown in Tables 2, 3, and 4, below, may be achieved.

Table 2. Change in body mass among groups.

	Mean change in body mass (g)			
Day	Group 1	Group 2	Group 3	Group 4
1	-7.66	4.14	-0.68	2.96
2	-8.52	6.20	1.64	3.26
3	-10.12	6.70	0.46	5.68
4	-9.54	7.32	0.78	8.50
5	-12.56	8.06	1.16	10.06
6	-14.02	7.74	0.94	10.51
7	-12.86	7.88	0.80	10.90
8	-14.42	10.22	4.00	11.38
9	-14.60	9.88	2.72	14.48
10	-14.72	10.90	2.98	14.46
11	-13.04	13.86	4.28	17.24
12	-12.22	17.46	7.30	19.64
13	-9.66	18.70	9.52	20.66
14	-9.12	20.32	9.54	23.22

Table 3. Change in fat mass among groups.

	Mean fat mass (g)			
Day	Group 1	Group 2	Group 3	Group 4
0	78.171	81.725	74.252	81.312
14	69.273	89.887	72.912	93.182
Change	-8.898	8.162	-1.340	11.870

Table 4. Change in lean mass among groups.

	Mean lean mass (g)			
Day	Group 1	Group 2	Group 3	Group 4
0	328.609	329.489	340.206	333.134
14	330.373	344.131	353.033	344.527
Change	1.764	14.642	12.827	11.393

Additionally, the food intake of each animal (mass of food the animal eats in one day) is measured daily during the fourteen-day experiment. Results of this study are shown in Table 5, below.

Table 5. Food intake among groups (P1).

	Mean daily food intake (g)			
Day	Group 1	Group 2	Group 3	Group 4
1	6.76	15.98	13.76	16.06
2	10.40	19.22	15.64	19.40
3	15.14	21.36	17.58	22.18
4	14.48	20.16	15.90	20.48
5	12.20	18.26	15.94	18.50
6	12.44	16.84	14.12	17.78
7	13.96	16.70	16.70	18.68
8	14.94	17.96	16.44	16.04
9	14.22	17.48	13.24	17.58
10	16.26	18.18	17.52	17.84
11	15.70	18.36	15.46	17.62
12	15.08	16.94	16.10	17.34
13	16.76	17.78	16.30	17.40
14	14.64	17.16	15.62	16.36

Continuous subcutaneous infusion of P1 in rats results in improved efficacy over single daily bolus dosing of equivalent P1 [0.044 mg/kg]. Cumulative weight loss in rats infused with P1 is significantly increased over both vehicle treated groups and rats dosed once daily. Decreased fat mass in rats continuously infused with peptide also indicates improved efficacy over daily dosing; however, the change does not reach significance between infused and daily dosed groups.

Experiments such as that described above may be performed on other MC4R agonists and for different time periods. For example, a seven-day study administering another peptide ("P2") may be performed. A stock solution of the MC4R peptide to be dose subcutaneous is prepared by dissolving 2 mg of P2 in 2 mL of the vehicle. This stock solution is then diluted 0.1 mg/mL using vehicle. This solution is subsequently referred to as P2sc solution. Both the P2sc solution and the vehicle are prepared fresh every three days and stored at 4°C in a sterile capped vial throughout the experiment. A second solution of the MC4R peptide P2 is prepared by dissolving 5 mg of P2 in 2.4 mL

of the vehicle prepared above. This solution is subsequently referred to as P2p solution. Ten ALZET® mini-osmotic pumps (Model 2001, 7-day payout at 1.0 μL/hour) are loaded using aseptic technique with either 200 μL P2 (n=4) or vehicle (n=4) solution and allowed to prime overnight in sterile 0.9% saline at 37°C in preparation for implantation into rats.

Sixteen rats are selected for this experiment. Ten rats are anaesthetized briefly with isoflorane (prepared above). Each anaesthetized rat is implanted with an ALZET® pump using sterile technique. The rats are divided into four groups of four rats: two groups containing pumps and two groups with no pumps. Experimental samples are administered to the rats as follows:

Table 6. Administration scheme for a P2 study.

Group	Substance	Delivery method	Approximate daily dose (μg/kg active)
1	MC4-R peptide P2	Sustained release via pump	50
2	Vehicle	Sustained release via pump	0
3	MC4-R peptide P2	Daily subcutaneous injection	50
4	Vehicle	Daily subcutaneous injection	0

Body mass is measured daily for seven days, and the cumulative change in body mass is calculated.

Using a procedure such as that described above, results shown in Table 7, below, may be achieved.

Table 7. Change in body mass among groups (P2).

	Mean change in body mass (g)			
Day	Group 1	Group 2	Group 3	Group 4
1	-5.52	7.03	5.50	5.88
2	-3.95	8.20	9.63	7.92
3	-10.53	1.30	5.20	4.72
4	-8.85	3.80	5.55	6.77
5	-11.35	2.60	7.43	8.82
6	-11.75	4.90	8.65	11.05
7	-13.73	6.60	9.73	12.88

Additionally, the food intake of each animal (mass of food the animal eats in one day) is measured daily during the seven-day experiment. Results of this study are shown in Table 8, below.

Table 8. Food intake among groups (P2).

	Mean daily food intake (g)			
Day	Group 1	Group 2	Group 3	Group 4
1	16.05	22.83	19.33	23.38
2	15.78	20.03	17.75	21.98
3	15.43	16.03	15.85	20.88
4	12.08	13.83	16.75	15.75
5	13.15	16.28	14.83	22.25
6	13.75	17.23	14.90	15.95
7	13.63	17.95	16.68	18.35

Continuous subcutaneous infusion of P2 in rats supports P1 study results. Infusion of peptide improved efficacy over single daily bolus dosing of equivalent P2 [0.05 mg/kg]. Cumulative weight loss in rats infused with P2 is significantly increased over both vehicle treated groups and rats dosed once daily.